DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/23/11 has been entered.

Receipt is acknowledged of the amendments and remarks filed on 05/23/11 and an IDS filed on 07/05/11. Claims 1-2, 5 and 13-15 have been amended and no claims have been cancelled or newly added. Accordingly, claims **1-19 and 23** are pending and under examination on the merits.

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Note: Claim 7 is missing “and” between the last two species of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeStefano et al (6,135,628) in view of Zhang et al (6,228,346).

DeStefano et al teach a method and apparatus for homogenizing aerosol formulations. Disclosed is a method and apparatus for homogenizing and micronizing aerosol formulations. The method includes the steps of homogenizing and micronizing an aerosol formulation at ambient temperature in a closed apparatus where the entire apparatus is maintained under elevated pressure. The apparatus includes a closed loop containing a reaction vessel, a homogenizer and a fluid conduit interconnecting the reaction vessel and the homogenizer. The homogenizer includes an interaction chamber and an intensifier pump. The interaction chamber includes a stream splitter for separating a stream of aerosol formulation components into two streams and an impaction chamber for recombining the stream (see abstract).

DeStephano et al teach a closed, pressurizable system for homogenizing aerosol formulations including the following components: (1) A pressurizable mixing vessel having inlet and outlet means; (2) A homogenizer disposed in fluid communication with the reaction vessel, said homogenizer including a plurality of nozzles having elongated orifices to eject under pressure sheets of the liquid to be homogenized, said nozzles being arranged to effect turbulent jet interaction of said sheets along a common jet interaction front and said sheets being ejected by said nozzles into a low-pressure zone filled with said liquid of the sheets along a common liquid jet interaction front and said sheets being ejected by said nozzles into a low-pressure zone filled with said liquid further creating turbulent jet interaction along a common boundary essentially defined and formed by said mixture in said low pressure zone and by said sheets ejected into said low pressure zone; jet interaction chamber-defining means arranged to provide

said low pressure zone of said liquid system in which said turbulent jet interaction is effected; pump means for delivering said liquid system under pressure to said nozzles; and (3) fluid conduits running from said outlet of said mixing vessel to the homogenizer and from the homogenizer back to the inlet of the mixing vessel, to form a closed apparatus therebetween.

The present invention is also directed to a method for homogenizing an aerosol formulation in a closed continuous-loop system under elevated pressure, the method including the steps of determining a desired level of homogenization, mixing an aerosol formulation in a mixing vessel, circulating the mixed aerosol formulation through a high pressure homogenizer, operating the high pressure homogenizer at a pressure sufficient to achieve homogenization of the mixed aerosol formulation, circulating the aerosol formulation back into the mixing vessel and repeating the aforementioned steps until the desired level of homogenization is achieved.

The closed continuous loop system may be connected by connecting means and conduit means to a high pressure filling station to fill aerosol containers. In an alternative embodiment, the closed continuous loop system may be used to prepare a concentrated aerosol formulation which is transferred by connecting means and conduit means to a large vessel where it is diluted with the aerosol propellant to a predetermined volume of aerosol formulation. Accordingly, the objects of the disclosure are to provide: -an improved method and system for homogenizing volatile mixtures,

- a method and system for homogenizing volatile mixtures, such as aerosol formulations comprising low boiling HFA propellants, at ambient temperature,

- a method and system which permit the preparation of aerosol formulations comprising a wide range of surfactants, including those surfactants which would not be miscible in the formulation if processed at reduced temperature,

And to provide a method and system which can both micronize particles of active substance in an aerosol formulation and homogenize the formulation, eliminating the need for prior milling of the active substance (see col. 4, lines 9-35).

DeStefano et al also teach the device which includes a high pressure homogenizer 12 that operates upon an aerosol formulation at a pressure sufficient to achieve homogenization and, where applicable and desired, the simultaneous micronization of solid particles present in the aerosol formulation. The high pressure homogenizer 12 may be, for example, a Microfluidics Model M-110F Microfluidizer® (see col. 5, lines 22-65).

DeStefano et al teach that the active ingredient may include for example, a pharmaceutically effective amount of a pharmaceutically active respiratory compound. Active ingredients include, for example, ipratropium bromide and albuterol sulfate. Possible surfactants include, for example, perfluorocarboxylic acid, polyethyleneglycols, polyethylene oxide sorbitan fatty acid ester, sorbitan esters, such as sorbitan monolaurate, sorbitan monooleate, sorbitan monopalmitate, and the like, polyvinylpyrrolidone, propylene glycol and oleic acid. A propellant is supplied to the reaction vessel 10, under pressure, through a valved inlet 11. The propellant may be, for example, a low boiling hydrocarbon; an HFA propellant such as HFA-227, HFA-134a or a combination of HFA-227 and HFA-134a; or a CFC propellant such as CFC 12 or

114, or a mixture thereof. The propellant may additionally comprise a solvent, such as for example an alcohol such as ethanol (see col. 6, lines 26-56).

DeStefano et al disclose that while carrying out the process of homogenization, or simultaneous homogenization and micronization, aerosol formulation flows through the components of the embodiment shown in FIG. 2 in the following sequence: starting from the mixing vessel 10, the formulation flows through the drain valve 50, conduit 30(c), the three-way valve 100, conduit 30(d), the high pressure homogenizer 12, the conduit 30(e), the three-way valve 101, conduit 30(f), the optionally present flow meter 170, conduit 30(i), by-pass connector 110, open by-pass valve 90, conduit 30(n), the optionally present flow meter 171, conduit 30(o), and then back into the mixing vessel 10. Once homogenization and, if applicable, micronization is complete, the flow of formulation is diverted from the homogenizer 12, to the pump 70, by way of conduit 30(g) and conduit 30(h), by operation of the three-way valves 100 and 101. The high pressure homogenizer 12 is removed from the circulation path of the aerosol formulation to avoid over-processing of the aerosol formulation. Up to this point the pump of high pressure homogenizer 12 is responsible for the circulation of formulation through the apparatus. Once the flow of formulation is diverted from the high pressure homogenizer 12, the pump 70 takes over this task. The pump 70, as well as the stirrer 40 of the reaction vessel 10, impart sufficient agitation to maintain suspension. Preferably, after about 15 minutes of circulation by the pump 70, when both the temperature and the pressure within the vessel increase to values which are close to their starting values, dispensing may begin (see col. 9, lines 10-40).

DeStefano et al lacks teachings on suspending the pharmaceutically active agent in a gaseous propellant or in a compressed gas. This deficiency is cured by Zhang et al.

Zhang et al teach that propellant gases with a low evaporation enthalpy, such as carbon dioxide, sulfur hexafluoride and ethane, can be used in the subcritical state in a pharmaceutical aerosol, without entailing the aforementioned disadvantages, if they are mixed with another gas that has a high evaporation enthalpy and a low vapor pressure, such as butane, propane or dimethyl ether. The added gas has two functions: to decrease the overall system's vapor pressure and to increase the system's dissolving capacity. The system's evaporation enthalpy is still sufficiently small, with the result that problems do not arise during evaporation. Due to the presence of non-inflammable gas, the system's inflammability is also substantially reduced. A special **propellant** mixture is prepared for pharmaceutical aerosols so as to **micronize the drugs** for pulmonary application. This propellant mixture is present in the subcritical state and contains at least one component from a first class of propellant gases and at least one component from a second class of propellant gases, with different enthalpy and vapor pressures (see summary).

Zhnag et al teach a pharmaceutical aerosol for pulmonary application; in addition to one or more pharmaceutical substances, this aerosol contains: 1) a propellant mixture in an amount of from 10 to 80 wt. %, and wherein the pharmaceutical may be present in the aerosol composition in a dissolved state (solution aerosol) or in a **suspended** state (suspension aerosol); 2) A drug; 3) A surfactant which is frequently

added in a suspension aerosol for enhanced suspension of the pharmaceutical. The conventional surfactants, such as oleic acid, lecithin and sorbitan trioleate, are used here. In consequence, such surfactants can be used without difficulty in the production of a suspension aerosol formulation.

The process produces particles generated by spraying, having a diameter of less than 8 µm, and preferably, the particle size is less than 5 µm. The percentages each relate to the total mass of the produced pharmaceutical particles "dried" after evaporating the propellant. These particles therefore have a smaller mass and are not so easily precipitated in the mouthpiece of the metered dose aerosol or in the spacer. Improved respirability means that not only the bronchial or upper pulmonary region, but also more deeply lying sections of the lungs and pulmonary alveoli are reached. This is not only a decisive advantage when the lung itself represents the affected organ to be treated, the resorption of systemic-action pharmaceuticals is also improved (see col. 4).

Zhang et al also teach that the pharmaceutical may be present in the aerosol composition as a solution or suspension with a percentage content of 0.01 to 5 wt. %, preferably 0.03 to 1 wt. %. For micronization, a spray nozzle common for this purpose is used. In a preferred embodiment of the newly developed pharmaceutical aerosol, the propellant mixture solely comprises one or more components from the above two classes. To achieve specific or improved effects, a combination of different active ingredients with varying percentage contents can be used in an aerosol formulation, e.g. combinations of ipratropium bromide and fenoterol, salbutamol and disodium cromoglicinic acid, and salbutamol and beclometason-17,21-dipropionate (see col. 5).

Zhang et al teach a device that comprises a gas cylinder, a high-pressure pump, a safety valve, a check valve, a spray nozzle, and an autoclave. The high-pressure pump is used to pump dimethyl ether, propane or butane out of the cylinder, which is positioned on a balance, into the autoclave. The feed quantity can be read off from the balance. After the pressure in the autoclave has reached the desired value, it is agitated for about 90 minutes. It is then not moved for 30 minutes, causing all the undissolved substances to separate from the gas mixture. A high-pressure viewing cell with a 35 ml volume is used to evaluate the stability of a suspension. The viewing cell has a large viewing diameter of 30 mm, making it much easier to observe the suspension conventional nozzles are used to process aerosols (see col. 5, line 59 to col. 6. line 30). The suitable nozzle aperture of a spray nozzle depends on the operating pressure (see col. 8, lines 34-37). Process of preparing particles is also exemplified in Examples 1-9.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have implemented the step of suspending particles in a gaseous propellant or in a compressed gas as taught by Zhang et al with the process of DeStefano et al on micronizing and homogenizing aerosol particulate formulations for inhalation with a reasonable expectation of successfully preparing dry powder particles in a suitable particle size with the known process of micronization and high pressure homogenization. Zhang et al teach that the gas system has two functions: to decrease the overall system's vapor pressure and to increase the system's dissolving capacity. In other words, the claims would have been obvious because the technique for improving

a particular formulation was part of the ordinary capabilities of a person of ordinary skill in the art, in view of the teaching of the technique for improvement in other situations.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 1-5, 8-12, 15-19 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mohsen et al (US 20080118442).

Mohsen et al teach pharmaceutical aerosol formulations of dihydroergotamine, or pharmaceutically acceptable salts thereof, to administer **dry powders and propellant suspensions** via pulmonary aerosol or nasal spray inhalation. The said aerosol formulations have superior stability, purity and comprise particle of respirable size particularly suitable for pulmonary delivery (see abstract).

It is disclosed that active compounds which are administered by inhalation must penetrate deep into the lungs in order to show topical, or alternatively, systemic action. In order to achieve this, the particles of the active compound must have a diameter which does not exceed approximately 0.5-5.8 μm mass mean aerodynamic diameter (MMAD) (see [0012]).

Mohsen et al disclose that in the MDI format the particles can be suspended/dispersed directly into a suspending media, such as a pharmaceutically acceptable **propellant**. Suitable suspending media is a propellant that does not serve as a solvent to the DHE particles such as 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA 227) either alone or in any combination. Carbon dioxide and alkanes, such as pentane, isopentane, butane, isobutane, propane and ethane, can also be used as propellants or blended with the said hydrofluoroalkane propellants. The DHE particulate dispersion may be achieved without surfactants or alternatively the DHE particulate dispersion may contain surfactants. Typical surfactants include the oleates, stearates, myristates, alkylethers, alkylarylethers, sorbates and other surfactants used by those skilled in the art of formulating compounds for delivery by inhalation, or any combination of the foregoing. Specific surfactants include, sorbitan monooleate (SPAN-80) and isopropyl myristate (see [0019]).

For formulations containing HFA227 plus surfactant, a mixing kettle (equipped with chilling jacket, a Silverstone **Homogenizer**, a Lightning Mixer, and a 4 port cover and situated on a weight scale) is chilled to 0 Celsius and blanketed with dry Nitrogen. After complete addition of the surfactant the homogenizer is energized and the mixture is sonicated for approximately 20 minutes. The drug powder is added to the vessel and continuously stirred at medium speed. After mixing for 20 minutes the mixture is pumped into canisters to fill approximately 50% weight in each canister. The valves are crimped on the top of each canister and the balance of the p227 is filled under pressure

through the stem of the valve to bring to 100% weight. The canisters are water tested, discharge tested, weigh checked and released for testing (see [0032]).

Mohsen et al do not anticipate the claimed process because the method steps are not disclosed as claimed. However adequate disclosure has been provided to one of ordinary skill in the art to make and use the invention as claimed. Mohsen et al teach inhalation of dry powder formulations comprising suspended active particles in a compressed gas, gaseous propellant or combination thereof in micron size. The suspension is also carried out by homogenization under pressure. "[w]hen an application simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious". KSR v. Teleflex, 127 S,Ct. 1727, 1740 (2007)(quoting Sakraida v. A.G. Pro, 425 U.S. 273, 282 (1976)). "[W]hen the question is whether a patent application claiming the combination of elements of prior art is obvious", the relevant question is "whether the improvement is more than the predictable use of prior art elements according to their established functions." (Id.). Addressing the issue of obviousness, the Supreme Court noted that the analysis under 35 USC 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." KSR v. Teleflex, 127 S.Ct. 1727, 1741 (2007). The Court emphasized that "[a] person of ordinary skill is... a person of ordinary creativity, not an automaton." Id. at 1742. Consistent with this reasoning, it

would have been obvious to have selected the process steps as claimed from the teachings of the .from within a prior art disclosure, to arrive at a product / process "yielding no more than one would expect from such an arrangement".

Response to Arguments

Applicant's arguments with respect to claim 1-19 and 23 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1-19 and 23 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINA HAGHIGHATIAN whose telephone number is (571)272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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